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Docking of 3,5-diphenyl- pyrazoline with monoamine oxidase A receptor and In-Silico structural property calculation

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ABSTRACT

Depression is one of the widely spread disorder in current population and is increasing exponentially. Now age group is not a mandatory clause for depression as children today are also affected. Inhibition of monoamine oxidase A (MAO A) isoform was reported for treating depression by elevating mood. Hydrazines have been also reported for their antidepressant action by inhibiting the monoamine oxidase. In this current study we have chosen 3,5-diphenyl-pyrazoline as ligand molecule which actually mimics the structure of cyclic hydarazine and was supposed to bind with MAO A receptor and inhibit it. Autodock software was used and standard protocol of docking was carried out by selecting grid of X:Y:Z (60:60:60). Other insilico properties were calculated using Molinspiration online property calculator, Protox II for structural property calculation and acute oral toxicity determination respectively. Results revealed though the ligand molecule was safe but not solely effective for MAO inhibition. Derivatization in the molecule is must increasing its biological potential.

Keywords: Depression, Docking, pyrazoline, Insilico toxicity determination

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INTRODUCTION

Depression is a common mental disorder that presents with depressed mood, loss of interest, or pleasure, decreased energy, feelings of guilts, disturbed sleep or appetite and poor concentration. While depression is the leading cause of disability for both males and female, the burden of depression is 50% higher for females than male (WHO 2008). It is the leading cause of disease for women in both high-income and low- and middle-income countries (WHO 2008)[1].Today, depression is estimated to affect 350 million people.

Monoamine oxidase (MAO) is a potent site for treating depression by elevating the mood of patients if these enzymes are inhibited. Moclobemide recall helped us to know more about MAO that it had two isoforms, MAO A and MAO B. Inhibition of MAO A helped the depression patients whereas inhibition of MAO B helped parkinson patients. Hydrazines have been reported for inhibitiig the MAO A iso-enzyme but have side effects.

Pyrazoline is a two heteroatom containing five membered heterocycle compound that has two nitrogen atom at 1,2 position[2]. The molecule has shown medicinally active property and is been reported in several peer reviewed journals[3]. The molecule selected as ligand posseses phenyl rings at 3 and 5 position. Pyrazolines mimic the structure of hydrazine in cyclic form. Aromatization of the pyrazoline molecule may increase the selectivity.

Objective

The objective of the current research is to screen the binding efficiency of 3,5-diphenyl-pyrazoline to MAO A receptor which is supposed to treat depression by inhibiting action of receptor and finally leading to elevation of mood. Another objective of study is predict structural and biological properties of ligand.

MATERIAL AND METHODS

a. Softwares and programs

Chemsketch a chemical molecule drawing tool was used to draw the ligand compounds[4]. Avogadro software was used to convert the .mol file to .pdb format[5]. Autodock 4.0 [6] a preliminary docking program was used for the semi-flexible protein ligand docking studies. Molinspiration online property calculator was used to study the chemical properties of the compound[]. The crystal structure of monoamine oxidase A receptor (MAO A) [PDB: 2Z5X] was downloaded from Protein Data Bank (PDB).

b. Preparation of ligand

Ligand structure was drawn using Chemsketch software and the structure was cleaned using the clean structure tool. The structure was saved in the working folder as .mol file. The .mol file was then accessed in Avogadro software and structure was optimized using optimization tool. The optimized structure was saved in the working directory as .pdb file.

c. Preparation of receptor

The crystal structure MAO A was downloaded in .pdb format from the online database and was rectified using Autodock v4.0 software. The energy was minimized by spreading the charges all over the receptor. The water molecules associated with receptor was deleted and polar hydrogen molecules were added.

d. Receptor-Ligand Docking

Autodock v4.0 was used to identify binding poses with associated binding energies. As per the inverse relation of energy and stability, the conformation with greater binding energy is less stable. The Default parameters of the software program have been applied similar to the protocol followed elsewhere [26-29]. Briefly, Lamarckian Genetic Algorithm (LGA) [30] with default atomic salvation parameters 126 Å (x, y, and z) grid box in ratio of (60:60:60) for scoring energy was set at co-ordinates as X = 34.741; Y = 28.104 and Z = -20.019 with 0.375 angstroms grid points spacing. Care was given during the grid box preparation to ensure that the active site of receptor was surrounded by the 3D grid box centered at its active ligand binding site location.

e. Online chemical property calculator

Molinspiration online property calculator[7] was used for calculating the properties of the ligand. The structure of the ligand was drawn using inbuilt tool and several properties were calculated. The properties were classified broadly into two types as structural property and bioactivity. Acute oral toxicity was predicted using Protox II web server[8].

RESULTS AND DISCUSSIONS

The structure of ligand and receptor was critically studied and drawn through insilico tools. The grid box of X:Y:Z (60:60:60) was made using Autodock v4.0 and is represented as in Fig 1a-c[9].

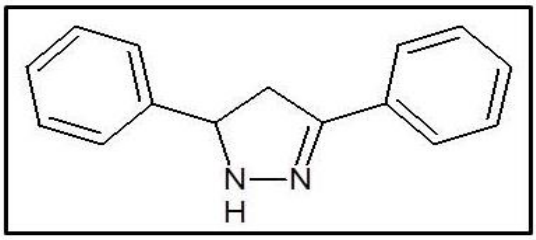

Fig 1a

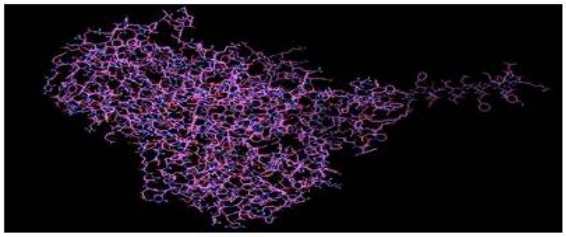

Fig 1b

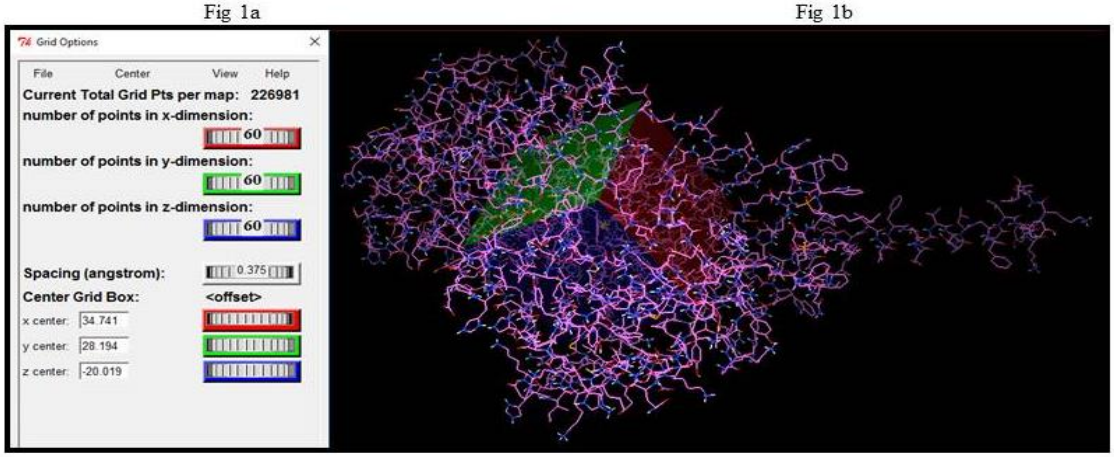

Fig 1c

Fig 1 a: Structure of ligand; b: Structure of receptor; c: Grid box

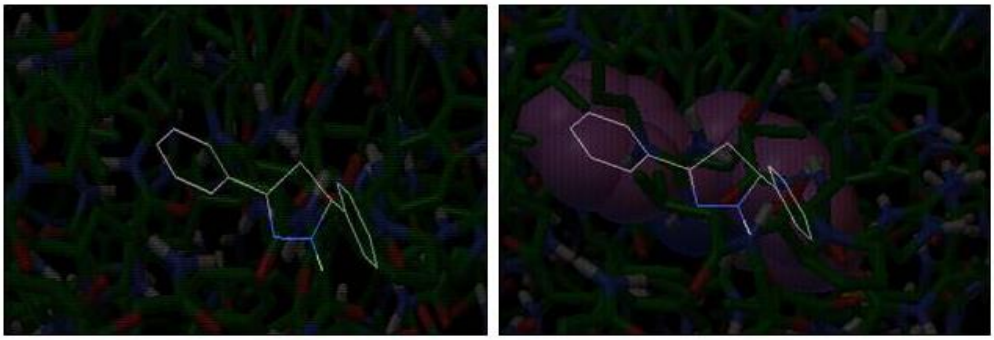

Fig 2: Docking of ligand with receptor

The result of docking Fig 2 shows that proposed ligand was adequately bound at the centre of the grid. On study of molecular interactions the amino acids with which ligand was showing interactions were TRP193; TYR410; ILE423; ARG424; PRO275; SER442; LEU298; TRP196; ALA409; ALA438; PHE411; THR437; GLU436 which is represented in Fig 3[10].

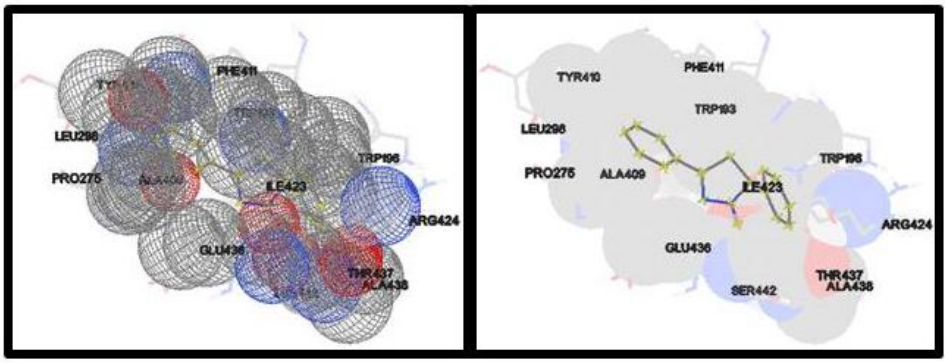

Fig 3: Molecular interactions of ligand with target

The mean binding energy of the best conformation was found to be + 18.34 and the root mean square deviation (RMSD) value was found to be 45.00. The free energy was found to be -1345.90 Kcal/mol[11].

The results of molinspiration online property calculator were represented as structural property and predicted bioactivity in table 1.

Table 1: Results of Molinspiration online property calculator

S. No.	Structural Property		Predicted Bioactivity	
	Property	Value	Site	Binding Efficiency
1	miLogP	3.32	GPCR ligand	-0.77
2	TPSA	24.39	Ion channel modulator	-0.93
3	natoms	17	Kinase inhibitor	-0.91
4	MW	222.29	Nuclear receptor ligand	-0.85
5	nON	2	Protease inhibitor	-0.99
6	nOHNH	1	Enzyme inhibitor	-0.53
7	nviolations	0		
8	Nrotb	2		
9	volume	213.90		

Finally the acute oral toxicity LD_{50} of the ligand molecule was predicted using insilico protocols of Protox-II software. The molecule belonged to class 4 and LD_{50} was found to be 1000 mg/Kg, which was supposed to be safe. There was no mutagenicity, hepatotoxicity and carcinogenicity predicted.

CONCLUSION

The pyrazoline molecule was successfully docked with MAO-A receptor and the molecular interactions were studied. Interpretation based on results revealed that the ligand did not showed best possible interaction. So, it can be suggested that pyrazolines solely might not show significant antidepressant activity and need further derivatizations. The results of property calculator predicted the structural and bioactivity. Acute toxicity values suggested the safety of the molecule.

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